Systematic Identification of Barriers to Human iPSC Generation.

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Public Summary:
Currently, if we lose a finger we cannot grow it back. One goal of regenerative medicine is to be able to teach remaining nearby mature cells to turn back into immature precursor cells, which can then be encouraged or "programmed" to develop into specific mature cell types; like finger cells. In this study, we identified many of the naturally occurring cellular barriers to such helpful cellular reprogramming. Reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) holds enormous promise for regenerative medicine. To elucidate endogenous barriers limiting this process,we systematicallydissected human cellular reprogramming by combining a genome-wide RNAi screen, innovative computational methods, extensive single-hit validation, and mechanistic investigation of relevant pathways and networks. We identify reprogramming barriers, including genes involved in transcription, chromatin regulation, ubiquitination, dephosphorylation, vesicular transport, and cell adhesion. Specific a disintegrin and metalloproteinase (ADAM) proteins inhibit reprogramming, and the disintegrindomain of ADAM29 is necessary and sufficient for this function. Clathrin-mediated endocytosis can be targeted with small molecules and opposes reprogramming by positively regulating TGF-b signaling. Genetic interaction studies of endocytosis or ubiquitination reveal that barrier pathways can act in linear, parallel, or feedforward loop architectures to antagonize reprogramming. These results provide a global view of barriers to human cellular reprogramming.

Scientific Abstract:
Reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) holds enormous promise for regenerative medicine. To elucidate endogenous barriers limiting this process, we systematically dissected human cellular reprogramming by combining a genome-wide RNAi screen, innovative computational methods, extensive single-hit validation, and mechanistic investigation of relevant pathways and networks. We identify reprogramming barriers, including genes involved in transcription, chromatin regulation, ubiquitination, dephosphorylation, vesicular transport, and cell adhesion. Specific a disintegrin and metalloproteinase (ADAM) proteins inhibit reprogramming, and the disintegrin domain of ADAM29 is necessary and sufficient for this function. Clathrin-mediated endocytosis can be targeted with small molecules and opposes reprogramming by positively regulating TGF-beta signaling. Genetic interaction studies of endocytosis or ubiquitination reveal that barrier pathways can act in linear, parallel, or feedforward loop architectures to antagonize reprogramming. These results provide a global view of barriers to human cellular reprogramming.